Severe Alcohol-Associated Hepatitis Is Associated With Worse Survival in Critically Ill Patients With Acute on Chronic Liver Failure

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Differences in mortality between critically ill patients with severe alcohol-associated hepatitis (sAH) and acute-on-chronic liver failure (ACLF) and non-sAH ACLF (i.e., ACLF not precipitated by sAH) are unknown. Such differences are important, as they may inform on prognosis and optimal timing of liver transplantation (LT). Thus, we aimed to compare short-term and longer-term mortality between patients with sAH ACLF and patients with non-sAH ACLF who were admitted to the intensive care unit. Patients with ACLF admitted from 2016-2018 at two tertiary care intensive care units were analyzed. SAH was defined by the National Institute on Alcohol Abuse and Alcoholism's Alcoholic Hepatitis Consortium and Model for End-Stage Liver Disease score >20. Mortality without LT was compared between sAH ACLF and non-sAH ACLF using Fine and Gray's competing-risks regression. A total of 463 patients with ACLF (18% sAH and 82% non-sAH) were included. Compared to patients with non-sAH ACLF, patients with sAH ACLF were younger (49 vs. 56 years; $P < 0.001$) and had higher admission Model for End-Stage Liver Disease (MELD) (35 vs. 25; $P < 0.001$) and Chronic Liver Failure Consortium (CLIF-C) scores (61 vs. 57; $P = 0.002$). There were no significant differences between the two groups for vasopressor, mechanical ventilation, and hemodialysis use. The cumulative incidence of death was significantly higher in patients with sAH ACLF compared to patients with non-sAH ACLF: 30-day 74.7% versus 45.3%; 90-day 81.9% versus 57.4%; 180-day 83.2% versus 63.0% (unadjusted subdistribution hazard ratio [sHR] 1.88 [95% confidence interval (CI) 1.44-2.46]; $P < 0.001$). After adjusting for CLIF-C score and infection in a multivariable competing-risk model, patients with sAH ACLF had significantly higher risk of death (sHR 1.57 [95% CI 1.20-2.06]; $P = 0.001$) compared to patients with non-sAH ACLF. *Conclusion:* Critically ill patients with sAH ACLF have worse mortality compared to patients with non-sAH ACLF. These data may inform prognosis in patients with sAH and ACLF, and early LT referral in potentially eligible patients. (*Hepatology Communications* 2022;6:1090-1099).

Acute on chronic liver failure (ACLF) is a syndrome defined by acute deterioration of liver function associated with extrahepatic organ failures[(1,2)] requiring intensive care unit (ICU) management[(3)] and high short-term mortality.[(1,4)] ACLF develops as consequence of intense

systemic inflammation[5] and occurs secondary to well-recognized precipitating events,[2,6] such as bacterial infections and severe alcohol-associated hepatitis (sAH). In patients with sAH, the development of ACLF is frequent with a prevalence of 48%,[7] and its development is associated with high short-term mortality at 54%.[7]

Beyond ICU supportive care for extrahepatic organ failures, management of sAH ACLF is challenging, as corticosteroids, the mainstay for sAH, are frequently contraindicated (or discontinued) due to worsening extrahepatic organ failures such as kidney failure and ongoing sepsis.[8] Furthermore, when corticosteroids are used, the probability of response is significantly reduced (particularly in patients with higher grades of ACLF) compared to patients without ACLF.[7,9] Corticosteroid use in sAH ACLF is also associated with an increased risk of infections, which negatively affects survival.[7,9] Therefore, patients with sAH ACLF may carry a different risk profile compared to critically ill patients with non-sAH ACLF (i.e., ACLF not precipitated by sAH). The differences in mortality between critically ill patients with sAH ACLF and patients with non-sAH ACLF remain unclear, particularly in a U.S.-based population where ICU admissions are not selective based on perceived futility of care.[10-13] Knowledge of these differences is important, as they may inform on prognosis and timely triaging for urgent liver transplant (LT) evaluation in patients with ACLF. Patients with ACLF who are LT eligible are already at a disadvantage in the current U.S. allocation system by Model for End-Stage Liver Disease (MELD) score.[14,15] Thus, differences in mortality risk in sAH ACLF compared with non-sAH ACLF could provide further insight on wait-list risk[16] and potential modifications of risk-based organ allocation.[14,16,17]

Given the importance of refining our understanding of risk in these patients, the aim of this study was to compare the cumulative incidence of short-term and longer-term mortality between critically ill patients with sAH ACLF and patients with non-sAH ACLF admitted to the ICU. Our secondary aims were to compare ACLF severity, organ failures, and advanced ICU therapies between the two groups.

Materials and Methods

STUDY POPULATION

Consecutive patients >18 years of age with cirrhosis or severe AH admitted with ACLF at two tertiary care academic ICUs at Indiana University Hospital from January 1, 2016, to December 31, 2018, were retrospectively analyzed. The diagnosis of cirrhosis was based on clinical parameters including laboratory tests, endoscopic/radiologic evidence of cirrhosis, and evidence of decompensation (e.g., ascites, hepatic encephalopathy, jaundice, variceal hemorrhage). ACLF and its grades were defined by the European Association for the Study of Liver's Chronic Liver Failure Consortium (CLIF-C).[2,18] Patients were excluded if they did not have ACLF, non-severe AH, or prior solid organ transplantation.

Severe AH was defined by clinical and laboratory criteria recommended by the National Institute on Alcohol Abuse and Alcoholism Alcoholic Hepatitis Consortia[19]: active alcohol use (>60 g of alcohol per day for men and >40 g of alcohol per day for women) for 6 months or more with <60 days of abstinence before the onset of jaundice, serum aspartate transaminase (AST) > 50 IU/mL, AST to alanine aminotransferase

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ratio >1.5, serum bilirubin >3.0 mg/dL, and Maddrey discriminant function >32 (or Model for End-Stage Liver Disease [MELD] score > 20). Information on alcohol intake was obtained from chart review (i.e., documentation from physicians and social workers) that was provided by the patient or their family/power of attorney if incapacitated. Patients were grouped as either sAH ACLF or non-sAH ACLF. Patients with non-sAH ACLF were those in whom ACLF was not precipitated by sAH (i.e., ACLF precipitated by bacterial infections).

This study was reviewed and approved by the institutional review board at our institution.

DATA COLLECTION

Patient demographic and clinical data, indication for ICU admission, corticosteroid therapy details, therapy for alcohol withdrawal (by chart review, either by physician documentation or use of alcohol withdrawal medication order sets), and use of ICU-specific interventions (i.e., use of vasopressors, mechanical ventilation, and hemodialysis) were collected. MELD,[20] CLIF-C, and Chronic Liver Failure (CLIF) organ failures scores[18] were calculated at the time of ICU admission. Given the potential predictive ability for prognosis[4] and for descriptive purposes, day 3 MELD, CLIF-C, and CLIF organ failure scores were also captured in patients with available data. Precipitants of ACLF were identified using the definitions described by the PREDICT study,[6] which included sAH, bacterial infections, gastrointestinal bleeding with shock, toxic encephalopathy, and therapeutic interventions. Infection that occurred during the ICU clinical course (second infections and fungal infections) was also identified. Death, cause of death, evaluation for LT, and LT were captured.

OUTCOMES

Patients were followed from the time of ICU admission up to 180 days to assess for outcomes (mortality and LT). The primary outcome was the mortality within 180 days.

STATISTICAL ANALYSIS

Patient demographic and clinical characteristics were compared by ACLF status (sAH ACLF and non-sAH ACLF). Continuous variables were presented as mean + SD and median with interquartile range where appropriate. Categorical variables were presented as percentages. Differences across groups with respect to categorical variables were analyzed using chi-square and Fisher's exact tests, whereas continuous variables were analyzed using Student t test or the Wilcoxon rank-sum tests between two groups, or Kruskal-Wallis test or analysis of variance among three groups.

Mortality with sAH ACLF and non-sAH ACLF was compared using Fine and Gray's competing-risks regression, with creation of a cumulative incidence function. LT was considered as the competing risk. Differences between cumulative incidence functions were determined using Gray's test. Multivariable competing risk analyses were performed to assess the association between sAH ACLF and mortality. Covariates chosen for multivariable modeling were selected *a priori* due to their clinical significance. These include age,[2,18] admission CLIF-C score,[18] admission MELD score,[21,22] presence of infection at time of ICU admission,[23,24] day 1 use of vasopressors,[23,25] and day 1 use of mechanical ventilation.[21,26] Day 1 hemodialysis was not included as a covariate as it was captured in either the CLIF-C or MELD score. A sensitivity analysis was performed for the primary outcome by excluding patients with ACLF and alcohol-associated cirrhosis (without evidence of AH), and patients with and without infection at the time ICU admission. Subdistribution hazard ratios (sHRs) with 95% confidence intervals (CIs) were calculated. A two-sided nominal P value < 0.05 was considered significant. Statistical analyses were performed using SAS 9.4 and SPSS, version 26.

Results

A total of 885 patients were screened during the study time period. After excluding those who did not meet the inclusion criteria (422 total patients: 419 patients without ACLF and 2 with non-sAH and without ACLF), a total 463 patients (17.9% sAH ACLF and 82.1% non-sAH ACLF) were included for analysis. The mean age was 57.3 + 11.8 years, and most were White (82.7%), male (59.2%), and directly admitted to the ICU (67.8%) from the emergency room department. The mean admission MELD and CLIF-C scores was 27.1 + 10.1 and 57.5 + 9.7, respectively. In the non-sAH ACLF group,

the most common etiologies of cirrhosis were alcohol (28.7%), non-alcoholic steatohepatitis (22.7%), hepatitis C (13.4), and alcohol with concurrent hepatitis C (10.6%). In addition to sAH as a precipitant (17.9%), infection (44.3%) and gastrointestinal bleed (25%) were the most frequent precipitants of ACLF. ACLF precipitants for each group can be found in Supporting Table S2.

SAH-ACLF TREATMENT DETAILS

Most of the sAH cases were probable (86.7%) followed by definite (9.6%) and possible (3.6%). The median Maddrey discriminant function score was 81.8 (59.3, 122.9). Corticosteroids were contraindicated in 77% of patients and used in 10%. The most common contraindications for corticosteroid use were kidney failure with concurrent infection (28.6%), kidney failure (22.2%), gastrointestinal bleed with concurrent kidney failure (14.3%), uncontrolled infection (11.1%), and combination of kidney failure, gastrointestinal bleed, and infection (9.5%). In those with corticosteroid use, treatment was stopped in 5 patients due to further decompensation/sepsis (n = 3) and an unfavorable Lille score (n = 2). Three patients responded to corticosteroid therapy. Fifty-seven percent were treated for alcohol withdrawal during their ICU course.

COMPARISONS OF CLINICAL CHARACTERISTICS STRATIFIED BY ACLF TYPE

Demographic and clinical characteristics of patients with sAH ACLF and non-sAH ACLF are compared in Table 1. Patients with sAH ACLF were significantly younger and more likely to be male when compared to patients with non-sAH ACLF: 48.6 + 12.0 versus 56.2 + 10.9 years ($P < 0.001$) and 69.5% versus 56.8% ($P = 0.029$), respectively. There were significant differences between the two groups for ACLF grades ($P < 0.001$), with higher grade-3 percentage in patients with sAH ACLF (66.2% vs. 42.2%). Accordingly, MELD score, CLIF-C ACLF score, and white blood cell count were significantly higher in patients with sAH ACLF compared to patients with non-sAH ACLF: 35.1 + 8.0 versus 25.3 + 9.7 ($P < 0.001$), 60.5 + 9.6 versus 56.9 + 9.6 ($P = 0.002$), and 15.6 + 9.0 versus 12.8 + 9.0 ($P = 0.001$), respectively. Comparisons between sAH ACLF, alcohol-associated

TABLE 1. COMPARISON OF DEMOGRAPHIC AND ADMISSION CHARACTERISTICS BETWEEN SAH ACLF VERSUS NON-SAH ACLF

Characteristic	Non-sAH (n = 380)	sAH (n = 83)	P Value
Age (SD)	56.2 (10.9)	48.6 (12.0)	<0.001
Gender, n (%) male	216 (56.8)	58 (69.5)	0.029
Race, n (%) White	316 (83.2)	67 (80.7)	0.175
BMI (SD)	30.6 (6.9)	30.2 (8.6)	0.854
Transfer from another hospital, n (%)	57 (15.0)	16 (19.3)	0.545
Direct admit to ICU, n (%)	262 (68.9)	52 (62.7)	0.91
SIRS, n (%)	315 (82.9)	76 (91.6)	0.109
Laboratory (SD)			
Sodium, mmol/L	134.7 (7.2)	131.6 (8.2)	0.002
Creatinine, mg/dL	2.3 (1.7)	3.0 (1.8)	0.03
INR	2.3 (1.5)	2.7 (1.1)	<0.001
Total bilirubin, mg/dL	5.3 (7.6)	16.9 (12.5)	<0.001
Albumin, g/dL	2.7 (0.6)	2.6 (0.6)	0.258
WBC, 10^9	12.8 (9.0)	15.6 (9.0)	0.001
Day 1 peak lactate, mmol/L	5.0 (5.0)	6.8 (6.9)	0.357
History of ascites, n (%)	195 (51.3)	43 (51.8)	0.935
History of hepatic encephalopathy, n (%)	207 (54.5)	31 (37.3)	0.005
MELD score (SD)	25.3 (9.7)	35.1 (8.0)	<0.001
CLIF- C organ failure score (SD)	11.7 (2.1)	12.1 (2.2)	<0.001
CLIF-C ACLF score (SD)	56.9 (9.6)	60.5 (9.6)	0.002
ACLF grade, n (%)			
Grade 1	97 (25.5)	8 (9.7)	<0.001
Grade 2	122 (32.1)	20 (24.1)	
Grade 3	161 (42.4)	55 (66.2)	
Reason for admission, n (%)*			
Grade 3/4 hepatic encephalopathy	89 (23.4)	27 (32.5)	0.083
Septic shock	104 (27.4)	24 (28.9)	0.775
Gastroesophageal variceal bleed	84 (22.1)	27 (32.5)	0.044
Severe AKI	50 (13.2)	16 (19.3)	0.149
Other liver related	27 (7.1)	9 (10.8)	0.249
Advanced therapies on day 1, n (%)			
Vasopressors	199 (52.4)	47 (56.6)	0.082
Mechanical ventilation	198 (52.1)	43 (51.8)	0.961
Hemodialysis	66 (17.4)	14 (16.9)	0.131
Presence of infection at admission, %	164 (43.2)	41 (49.4)	0.3

*Not mutually exclusive.
Abbreviations: AKI, acute kidney injury; BMI, body mass index; INR, international normalized ratio; SIRS, systemic inflammatory response; WBC, white blood cell count.

cirrhosis ACLF (without clinical evidence of AH), and non-alcohol-associated cirrhosis ACLF can be found in Supporting Table S1.
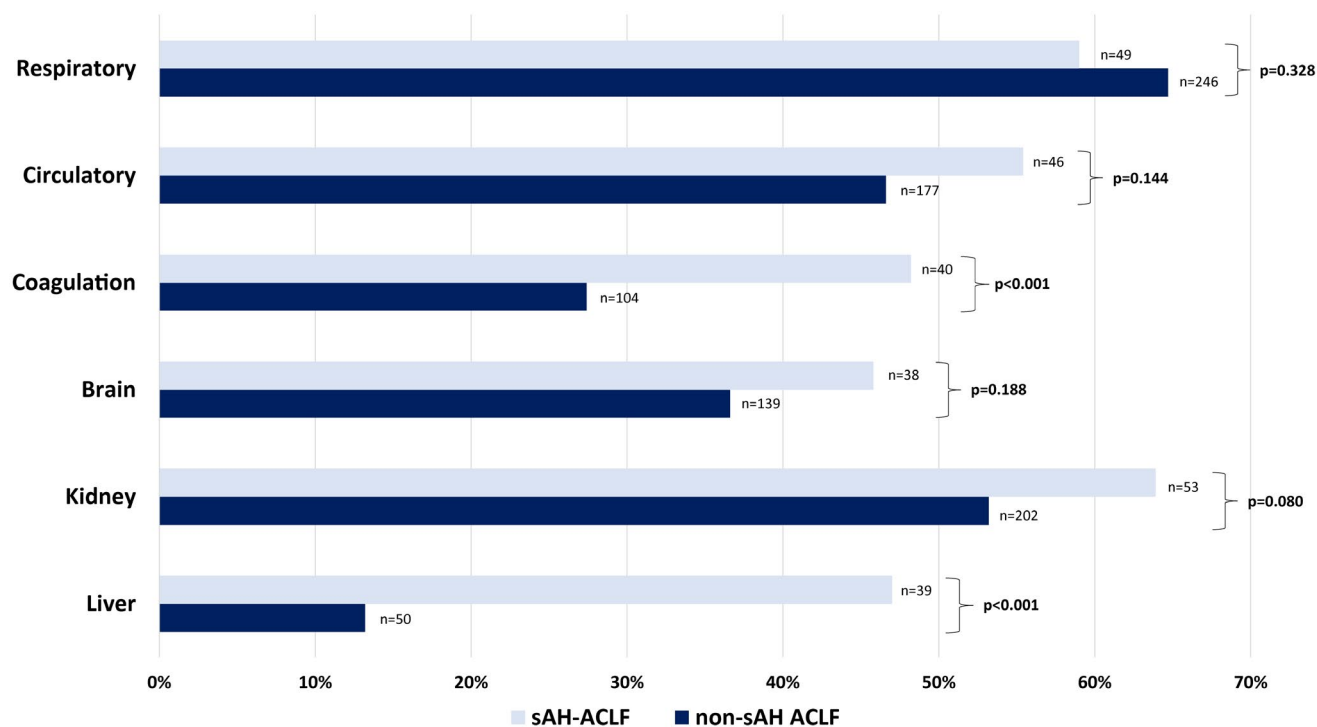
FIG. 1. Comparisons of organ failures between sAH ACLF and non-sAH ACLF.

Comparisons of organ failures at the time of ICU admission between patients with sAH ACLF and patients with non-sAH ACLF are shown in Fig. 1. Patients with sAH ACLF had higher liver and coagulation failure compared to patients with non-sAH ACLF: 47.0% versus 13.2% ($P < 0.001$) and 48.2% versus 27.4% ($P < 0.001$), respectively. However, there were no significant differences between the two groups for ICU advanced therapies on day 1 (Table 1).

Both groups had similar rates of infection at the time of ICU admission (n = 41 [49.4] sAH ACLF vs. n = 164 [43.2%] non-sAH ACLF; $P = 0.309$). Overall, 76.8% (n = 157) were culture positive (n = 35 [85.4%] sAH ACLF and n = 122 [74.4%] non-sAH ACLF), of which 20.5% were multidrug resistant organisms (n = 11 [26.8%] sAH ACLF and n = 31 [18.9%] non-sAH ACLF). Infections by site and organism can be found in Supporting Table S3. Furthermore, patients with sAH ACLF had significantly higher rates of gastroesophageal variceal bleed compared to patients with non-sAH ACLF (n = 27 [32.5%] vs. n = 84 [22.1%]; $P = 0.044$). Thus, in combination with infections, patients with sAH ACLF had significantly more precipitants compared to patients with non-sAH ACLF

(>1 precipitant: 71% sAH ACLF vs. 59% non-sAH ACLF; $P < 0.001$).

COMPARISONS OF ICU CLINICAL COURSE STRATIFIED BY ACLF TYPE

Patients with sAH ACLF had significantly higher day 3 white blood cell counts and MELD scores compared to patients with non-sAH ACLF: 15.3 + 7.5 versus 11.3 + 7.5 ($P < 0.001$) and 34.8 + 8.3 versus 28.7 + 9.5 ($P < 0.001$), respectively. However, day 3 CLIF-C ACLF scores were similar between the two groups (Table 2). Patients with sAH ACLF had numerically higher rates of vasopressor and mechanical ventilation use: 67.5% versus 56.8% and 73.5% versus 62.6% (although these differences were not statistically significant). There were no significant differences between the two groups for duration of vasopressor use, mechanical ventilation, and ICU length of stay (Table 2). However, ICU survival was significantly lower in patients with sAH ACLF compared to patients with non-sAH ACLF (42.2% [n = 35] vs. 66.8% [n = 254]; $P < 0.001$. Comparisons between

TABLE 2. COMPARISON OF ICU CLINICAL COURSE BETWEEN SAH ACLF VERSUS NON-SAH ACLF

Characteristic	Non-sAH (n = 380)	sAH (n = 83)	P Value
Day 3 WBC (SD)*	11.3 (7.5)	15.3 (7.5)	<0.001
Day 3 MELD (SD)†	28.7 (9.5)	34.8 (8.3)	<0.001
Day 3 CLIF-C organ failure score (SD)†	12.3 (2.7)	13.7 (2.8)	0.030
Day 3 CLIF-C ACLF score (SD)†	57.5 (11.5)	59.8 (11.9)	0.059
Advanced therapies during ICU course, n (%)			
Vasopressors	216 (56.8)	56 (67.5)	0.055
Mechanical ventilation	238 (62.6)	61 (73.5)	0.052
Hemodialysis	100 (26.3)	24 (28.9)	0.628
Second infection, n (%)	44 (11.6)	12 (14.5)	0.471
Evaluated for LT	67 (17.6)	8 (9.6)	0.073
Duration of vasopressor use, median days (IQR)	2 (1, 4)	4 (1, 6)	0.577
Duration of mechanical ventilation, median days (IQR)	4 (1, 7)	4 (2, 8)	0.283
ICU length of stay, median days (IQR)	5 (2, 9)	6 (2, 11)	0.181

*Available in 284 patients (sAH: 54; non-AH: 230).
†Available in 147 patients (sAH: 40; non-AH: 107).
Abbreviations: IQR, interquartile range; SIRS, systemic inflammatory response; WBC, white blood cell count.

both groups in ICU survivors can be found in Supporting Table S5. The rates of second infections were similar between the two groups (Supporting Table S3). Fungal infections were infrequent and occurred in 6.3% (n = 9 [10.8%] sAH ACLF vs. n = 20 [5.2%] non-sAH ACLF; *P* = 0.693). Details with regard to fungal infections (by site and organism) can be found in Supporting Table S4. Patients with non-sAH ACLF were more likely to be evaluated for LT compared to patients with sAH ACLF (17.6% vs. 9.6%), but these differences were not significant.

COMPARISONS OF CUMULATIVE INCIDENCE OF DEATH BY ACLF TYPE

A total of 334 patients died (n = 73 [88.0%] sAH ACLF and n = 261 [68.7%] non-sAH ACLF); 24 patients were transplanted (n = 2 [2.4%] sAH ACLF and n = 22 [5.8%] non-sAH ACLF); and 5 patients (n = 1 [1.2%] sAH ACLF and n = 4 [1.1%] non-sAH ACLF) were lost to follow-up during the study period. The most common causes of death were multiorgan failure (51.7%), septic shock (18.2%), and liver failure (10.3%).

Comparisons of cumulative incidence for mortality between both groups can be found on Fig. 2 and Table 3. The probability of mortality was significantly higher in patients with sAH ACLF compared to patients with non-sAH ACLF (unadjusted sHR

1.88 [95% CI 1.44, 2.46]; *P* < 0.001). In addition, the median time to death was significantly shorter in patients with sAH ACLF compared to patients with non-sAH ACLF (11 [6, 14] days vs. 46 [30, 69] days; *P* < 0.001).

The cumulative incidence of mortality by ACLF grade in each group can be found in Table 4. In both groups, the probability of death significantly increased with ACLF severity, with the highest probability in grade 3 ACLF. Furthermore, in all ACLF grades, patients with sAH ACLF had higher incidence of mortality at 30, 90, and 180 days compared to patients with non-sAH ACLF.

Three multivariable competing risk models were created to evaluate the association between sAH ACLF and risk for mortality (model 1: admission CLIF-C ACLF score and presence of infection at time of ICU admission; model 2: age, admission MELD score, and presence of infection at time of ICU admission; and model 3: age, admission MELD score at time of ICU admission, presence of infection at time of ICU admission, day 1 vasopressor use, and day 1 mechanical ventilation use). On all models, sAH ACLF was independently associated with an increased risk for death (model 1: sHR 1.57 [95% CI 1.20, 2.06]; *P* = 0.001; model 2: sHR 1.59 [95% CI 1.16, 2.17]; *P* = 0.004; and model 3: sHR 1.63 [95% CI 1.18, 2.23]; *P* = 0.003). The sHR for sAH ACLF was unchanged when gastrointestinal bleed was added as a covariate to all three models (model 1: sHR
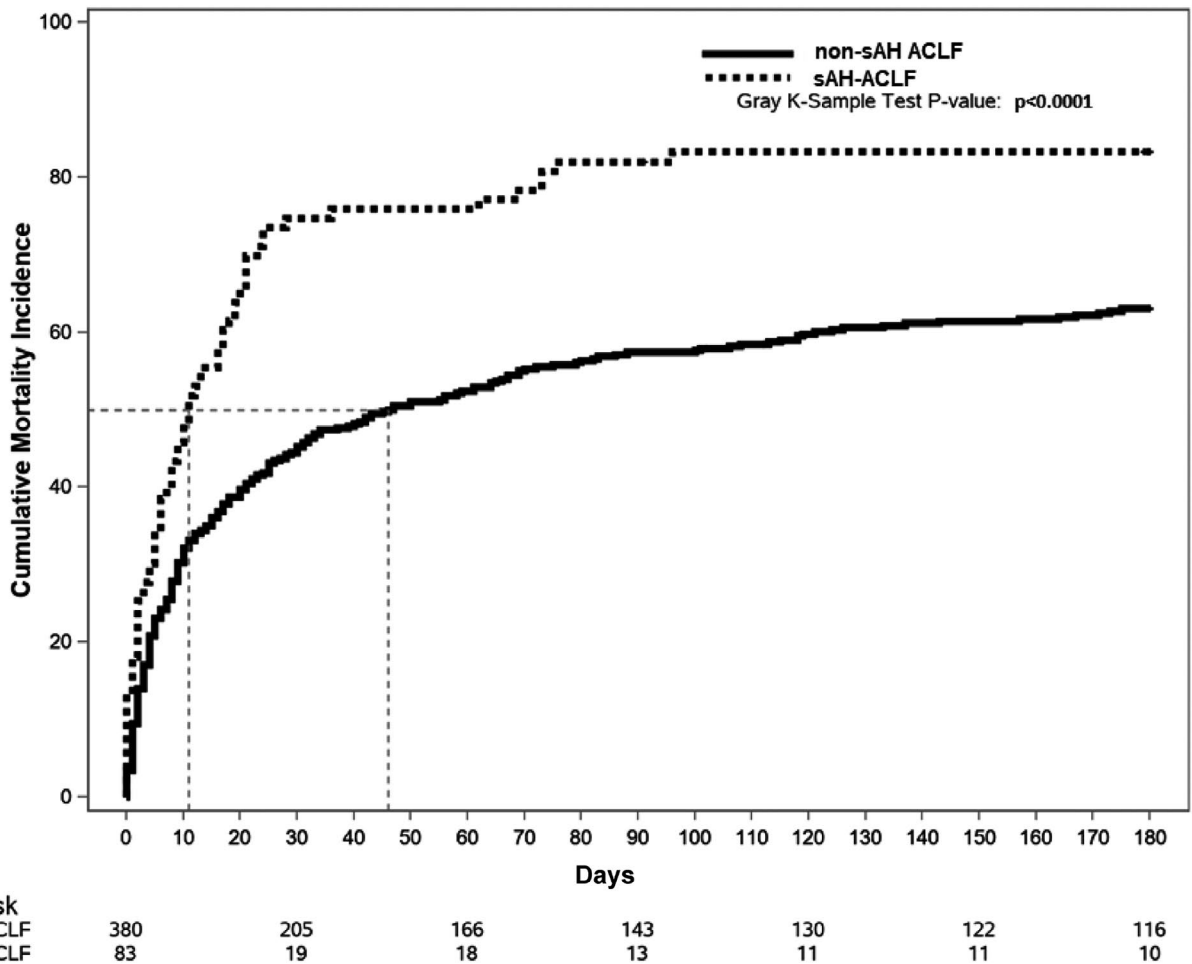
FIG. 2. Comparisons of cumulative incidence of mortality between sAH ACLF and non-sAH ACLF. Intersection of dotted lines provides median days to death in each group.

TABLE 3. COMPARISONS OF CUMULATIVE INCIDENCE OF MORTALITY BETWEEN SAH ACLF AND NON-SAH ACLF

ACLF Type	30-Day (95% CI)	90-Day (95% CI)	180-Day (95% CI)	sHR (95% CI)	P Value*
Non-sAH	45.3 (40.5-50.6)	57.4 (52.6-62.6)	63.0 (58.3-68.1)	Reference	<0.001
sAH	74.7 (65.8-84.6)	81.9 (73.9-90.8)	83.2 (75.4-91.9)	1.88 (1.44, 2.46)	

*Gray's k-sample test for equality of cumulative incidence functions.

1.61 [95% CI 1.23, 2.11], P = 0.001; model 2: sHR 1.63 [95% CI 1.19, 2.24], P = 0.002; and model 3: sHR 1.69 [95% CI 1.22, 2.33], P = 0.002). Sensitivity analysis showed similar results when patients with ACLF and alcohol-associated cirrhosis and patients with and without of infection at time of admission were removed from the analysis.

Discussion

In this study of critically ill patients with ACLF, we found patients with sAH were younger, had higher rates of hepatic and coagulation organ failure, but had similar rates of infections and durations of ICU advanced therapies compared to patients with without

TABLE 4. CUMULATIVE INCIDENCE OF MORTALITY STRATIFIED BY ACLF GRADE IN SAH ACLF AND NON-SAH ACLF

ACLF Type	30-Day (95% CI)	90-Day (95% CI)	180-Day (95% CI)	sHR (95% CI)	P Value*
Non-sAH ACLF					
Grade 1	18.6 (12.2-28.2)	32.0 (23.9-42.8)	40.5 (31.7-51.7)	Reference	
Grade 2	33.6 (26.2-43.2)	50.0 (41.8-59.8)	55.8 (47.2-65.5)	1.62 (1.12, 2.35)	
Grade 3	70.2 (63.4-77.7)	78.3 (72.1-85.0)	82.0 (76.2-88.2)	3.88 (2.75, 5.47)	<0.001
sAH-ACLF					
Grade 1	50.0 (23.1-100.0)	75.0 (45.8-100.0)	75.0 (45.8-100.0)	Reference	
Grade 2	60.0 (41.3-87.1)	65.0 (46.4-91.0)	70.0 (51.7-94.7)	1.15 (0.54, 2.49)	
Grade 3	83.6 (74.1-94.4)	89.1 (80.9-98.2)	89.1 (80.9-98.2)	2.27 (1.20, 4.31)	0.029

*Gray's k sample test for equality of cumulative incidence functions.

AH. Despite these similarities, patients with sAH ACLF had significantly higher incidence of short-term and longer-term mortality compared to patients with non-sAH ACLF. These differences persisted when adjusting for clinically relevant characteristics: Patients with sAH ACLF are 1.5-1.6 times at higher risk for death compared to patients with non-sAH ACLF.

The high rate of mortality observed in patients with sAH ACLF is not unexpected and in line with a previous study.[7] However, we found higher incidence of short-term and longer-term mortality in comparison to non-AH-ACLF. These differences are likely attributed to the severity of ACLF observed in our study, in which most patients with sAH had either ACLF grade 2 or 3. Additionally, our study population only consisted of ICU patients, a clinical setting where patients are sicker and have multiple extrahepatic organ failures requiring advanced therapies.

The most common precipitants for the development of ACLF are infections, sAH, and gastrointestinal hemorrhage.[6] A recent multicenter observational study from Europe showed that a single unique precipitant for the development of ACLF (i.e., infection alone vs. sAH alone) had similar rates of mortality, whereas the cumulative number of precipitants in an individual is associated with worse mortality.[6] Our study validates these findings and explains the higher rates of mortality found in patients with sAH ACLF. We found that 71% of patients with sAH ACLF had two or more precipitants compared to 59% in patients with non-sAH ACLF. The degree of systemic inflammation, which increases in parallel to the number or precipitants, also explain our findings.[6] Systemic inflammation is a known driver of organ failures and

mortality in patients with sAH.[27] Although we were unable measure unique biomarkers of inflammation in ACLF (e.g., C-reactive protein,[2,6] tumor necrosis factor alpha,[28] interleukin 6[28]), we did find significantly higher white blood cell counts and higher percent of systemic inflammatory response syndrome in patients with sAH ACLF.

LT as a rescue therapy in sAH is advocated by current guidelines in highly selected patients with favorable psychosocial profiles.[8,29] However, the role and timing of LT in sAH ACLF is unclear.[30] LT evaluation of patients with sAH without ACLF is rigorous,[31] and a primary criterion to be considered is whether a patient knew about their liver disease or had prior episodes of AH.[8,30] Obtaining this information, as well as a detailed psychosocial assessment, requires active patient engagement. In critically ill patients with sAH ACLF, such assessments are challenging due to the nature of the clinical setting (i.e., a patient may be mechanically ventilated, encephalopathic, or in alcohol withdrawal). Our study highlights that the window to obtain this important information is narrow, given that the median time to death is about 11 days. A retrospective U.S. study (Accelerate-AH) evaluating LT in sAH reported a median time of 13 days from hospitalization to listing with additional 7 days to LT.[32] Our data build on these observations and shed light on the observed high risk for death in patients with sAH ACLF who require ICU care, where the time to LT evaluation is more urgent with a limited window of opportunity. Hence, the results from our study could inform on timing and design of protocols for urgent LT evaluation in patients with sAH ACLF.

Our study has several limitations. Due to the retrospective nature of the study, we could not assess the decisions surrounding the support for or barriers against LT evaluation. Knowledge of these decisions would be informative, as it would provide insight on specific psychosocial issues that are absolute barriers for LT as well as to better characterize futility in real time.[30] Similarly, we were unable to control for other potential confounders such as frailty[33,34] and malnutrition.[35,36] Also, our study was performed at two tertiary care academic hospitals. Therefore, it is not known whether results could be extrapolated to other centers across the United States. Hence, a prospective multicenter study with strict protocols is needed to confirm our findings.

Despite the limitations in our study, there also several strengths. Our sAH-ACLF sample size was large, which allowed for meaningful comparisons between sAH ACLF and non-sAH ACLF. These comparisons allowed better understanding on ACLF severity, ICU clinical course, and short-term and longer-term outcomes between these groups. In addition, the limited number of LTs for sAH at the study centers during the study period allowed us to examine the natural history of sAH ACLF. Similarly, given the unrestricted approach to ICU admission at our center (and across most U.S.-based ICUs where refusal for futility occurs infrequently[13]), we were able to provide accurate estimates of mortality risk.

In conclusion, despite having similar rates of infections and durations of ICU advanced therapies between patients with sAH ACLF and patients with non-sAH ACLF, patients with sAH ACLF are younger and have significantly higher short-term and longer-term mortality compared to patients with non-sAH ACLF. Drivers of mortality in sAH ACLF are likely related to higher number of precipitants observed in this patient population. Therapeutic interventions are in critical need for this at-risk population. Where possible, patients with sAH ACLF should be evaluated for LT during their ICU course, as they are very unlikely to survive beyond 30 days. Further multicenter and prospective studies are needed to validate our findings, which ultimately could define an optimal window for LT in critically ill patients with sAH ACLF.

Author Contributions: Study concept and design: K.R.P. and M.S.G. *Data analysis:* K.R.P., F.P., and M.S.G. *Manuscript preparation:* K.R.P. and M.S.G. Critical manuscript review: All authors.

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